	ANTIVIRAL			
	Amantadine (Symmetrel®)	**Rimantadine (Flumadine®)**	**Zanamivir (Relenza®)**	**Oseltamivir (Tamiflu®)**
FDA Indications	Type A Only **Treatment** (All patients ≥ 1yr) **Prophylaxis** (All patients ≥ 1yr)	Type A Only **Treatment** (ages ≥13 yrs) **Prophylaxis** (All patients ≥ 1 year)	Type A and B **Treatment ONLY** (ages ≥ 7 years)	Type A and B **Treatment** (all patients ≥ 1 yr) **Prophylaxis** (Pts ≥ 13 years)
Available Dosages	100 mg capsules and tablets 50mg/5ml syrup	100mg tablets 50mg/5ml syrup	Powder for inhalation: Diskhaler® 4 x 5mg doses per Rotadisk® 5 Rotadisks per package	75 mg Capsules Powder for oral suspension: 12mg/ml (25 mls) tutti frutti flavor; must be refrigerated, expires in 10 days
	Treatment **Initiate antiviral therapy as soon as possible after onset of symptoms. Treatment must begin within 48 hours of symptom onset.**			
Treatment Dosing	Ages 1–9: 5mg/kg up to 150mg in 2 divided doses Age 10 to 64: 100mg bid Age >65: ≤ 100mg daily Discontinue after 3 to 5 days; or 24 to 48 hours after the disappearance of symptoms	Ages 13-64: 100mg bid Age > 65: ≤ 100mg daily Discontinue after 3 to 5 days; or 24 to 48 hours after the disappearance of symptoms	Age 7 and older: 10mg every 12 hours x 5 days Patients must be trained in use of Diskhaler ® Two doses should be taken on the first day of therapy regardless of interval; subsequent doses should be taken every 12h	Ages 1-12: <15kg: 30mg bid x 5 days ≥ 15kg-23kg: 45mg bid x 5 days >23-40kg: 60mg bid x 5 days >40kg: 75mg bid x 5 days Age 13 and above: 75mg bid x 5 days
	Prophylaxis			

Prophylaxis Dosing	Ages 1- 9: 5mg/kg up to 150mg in 2 divided doses Age 10 to 64: 100mg bid Age >65: ≤ 100mg daily In institutions: give for duration of outbreak In individuals at risk of serious complications (ie: pt is in household in which someone has been diagnosed with the flu): give x 7 days	Age 1-9: 5mg/kg up to150mg in 2 divided doses Age 10 to 64: 100mg bid Age >65: ≤ 100mg daily In institutions: give for duration of outbreak In individuals at risk of serious complications (ie: pt is in household in which someone has been diagnosed with the flu): give x 7 days	Not approved	Ages 13 and above: 75mg once daily x 10 days In community outbreaks: prophylaxis may be continued for up to 6 weeks.
	Dosing should be discontinued as soon as possible to avoid development of resistance			Take with food
Renal Considerations (Note: With each decade of life, there is a dramatic decline in creatinine clearance. Thus, doses of drugs cleared renally should be adjusted for advanced age)	CrCl 30-50ml/min: 200mg day 1, 100mg daily CrCl 15-29ml/min: 200mg on day 1, 100 mg QOD CrCl < 15ml/min or hemodialysis: 200mg every 7 days	CrCl <10ml/min: 100mg once daily	No dosage adjustment required	CrCl 10-30ml/min: Treatment dose 75mg daily x 5 days Prophylaxis dose: 75mg QOD CrCl < 10ml/min: No information available
Hepatic Dosing Considerations	No dosage adjustment required	Reduce dosage to 100mg per day in patients with severe hepatic disease	No dosage adjustment required	No dosage adjustment required
Side Effects	CNS: nervousness, anxiety, difficulty concentrating, lightheadedness GI: nausea and loss of appetite, xerostomia, diarrhea or constipation CV: orthostatic hypotension, peripheral edema Respiratory: dry nose	CNS: (less than with amantadine) nervousness, anxiety, difficulty concentrating, lightheadedness GI: nausea and loss of appetite	Respiratory: (2%) decreased respiratory function and bronchospasms especially in pts with lung disease CNS: headache (2%) Dizziness (2%) GI: nausea (3%) diarrhea (3%)	GI: nausea and vomiting (10%) CNS: insomnia (1%) vertigo (1%) The following side effects were seen more frequently when used for prophylaxis: headache (20%) fatigue (8%) cough (6%) and diarrhea (3%)
Precautions	Use with caution in patients with liver disease, history of recurrent and eczematoid dermatitis, uncontrolled psychosis or sever psychoneurosis, seizures	Use with caution in patients with hepatic and renal dysfunction. Avoid use, if possible, in patients with recurrent and eczematoid dermatitis, uncontrolled	Bronchospasm, decreased lung function, and other serious adverse reactions, including those with fatal outcomes have been	Safety and efficacy have not been established in the treatment of patients less than 18 yrs old or in immuno-

	and in those receiving CNS stimulant drugs. Amantadine has been associated with neuroleptic malignant syndrome. Use with caution in patients with CHF, peripheral edema, or orthostatic hypotension. Avoid use in patients with untreated angle closure glaucoma	psychosis, or severe psychoneurosis.	reported. If used in patients with underlying lung disease, proper supportive measures including short acting bronchodilators should be available. Patients must be instructed in proper use No data to support the use after 48 hours of symptoms or in patients with significant underlying medical conditions	compromised patients Safety and efficacy have not been established in the prophylaxis of patients less than 13 yrs old
Pregnancy Rating	Category C	Category C	Category C (Investigational: for prophylaxis in pregnancy)	Category C
Contraindications	Hypersensitivity to amantadine or any component	Hypersensitivity to drugs in amantadine class or any component of the product	Not recommended in persons with underlying airway disease	Hypersensitivity to oseltamivir or formulation
Pharmacokinetics	Excreted unchanged in urine by glomerular filtration and tubular secretion	75% metabolized and excreted by kidneys	4 to 17% systemically absorbed. Excreted unchanged in urine. Unabsorbed drug is excreted in feces	80% absorbed and metabolized by hepatic esterases to active form, oseltamivir carboxylate. Excreted in urine by glomerular filtration and tubular secretion. Not metabolized through CYP450 system
Drug Interactions	Careful observation of patients receiving concurrent CNS active drugs, both depressants and stimulantsn is recommended. Concurrent administration of antihistamines or anticholinergics can increase CNS side effects. Concurrent use of HCTZ, triamterene or trimethoprim can increase the toxicity of amantadine	None noted	None noted	Probenecid increases serum concentrations by 2 fold. Potential exists for interaction with any medication secreted by the glomerular filtration and tubular secretion
Food Interactions	None noted	None noted	None noted	Take with food to improve tolerance

Formulary Status in RI (BC, Coastal, United)	BC- yes United-yes	BC-yes United-yes	BC-yes- third tier United-yes	BC-yes-third tier United-yes
Generic availability	Yes	Yes	No	No
Approximate Retail Cost (Based on local RI retail pharmacies accessed 10/22/04. Prices may vary)	$9.99 (10 capsules)	$ 24.19 (10 tablets)	$77.59 (1 Diskhaler)	$90.59 (10 capsules packaged as dispensing unit)
Clinical Benefit (select key clinical trials from the primary literature to discuss the "evidence" for its role in primary care)	Clinical trials using amantadine 200mg/day to treat influenza type A within 48 hours of onset of symptoms showed a reduction of days with fever by approx.1 day. There is less data examining the efficacy of rimantadine. Rimantadine is similar to amantadine in its antiviral activity and provides similar treatment benefit. In children, some trials showed benefit, other no difference between amantadine or rimantidine and acetaminophen. There is no evidence showing a reduction in pneumonia or otitis media. Resistance to amantadine and rimantadine is seen with a frequency of about 50% in children, the elderly and in immunocompromised patients. Resistance poses a major problem when these drugs are used therapeutically and prophylactically at the same time in close contact environments.		There are 7 RCT trials examining the efficacy of zanamivir in mostly healthy individuals ages 12 to 65 years. The intention to treat analyses consistently showed a reduction in duration of symptoms by approximately 1 day. Two trials assessed time to resumption of normal activity and demonstrated that the use of zanamavir reduced the length of time to resumption of normal activity by 1.3-2 days. Trials in high risk individuals are limited. A retrospective pool of high risk patients from efficacy studies demonstrated a significant reduction both in intention to treat and flu positive populations with time to alleviation of symptoms being 1.5days to 2.5days, respectively, and the reduction in length of time to resumption of normal activities being 2 and 3 days, respectively	Two large double-blind, placebo-controlled RCT's of naturally occurring influenza have been performed. Oseltamivir treatment over 5 days, started within 36 to 48 hours after onset of symptoms, reduced the time to alleviation of symptoms by approx. 1 day in the intention to treat population and by 33 hours in flu positive patients. An open label study demonstrated the enhanced efficacy of earlier treatment. Tx started within 12 hours of onset of symptoms reduced the total mean illness duration by 3 days more, compared to tx started after 48 hours (108 hours of illness duration for earlier treated patients versus 183 hours for patients treated within 48 hours). The study demonstrated that for every six-hour interval of earlier treatment, the duration of flu illness was decreased by 10 hrs
Role in therapy	The CDC recommends use of amantidine or rimantidine for chemoprophylaxis in adults.	The CDC recommends use of amantadine or rimantidine for chemoprophylaxis in adults.	The CDC recommends the use of zanamivir as an option for the treatment of children ≥	The CDC recommends the use of oseltamivir as an option for treatment of

	Amantadine is also an option for treatment of children aged 1 – 12 years. The use of this agent is limited due to the rapid development of resistance.	Rimantidine could be preferred over amantadine due to the possibility of less CNS side effects	7 yrs old and for the treatment of adults with influenza type A or B who present within 48 hours of symptom onset.*	children > 1 yr old and for the treatment of adults with influenza type A or B who present within 48 hrs of symptom onset.* The Coastal Clinical Practices Committee recommends using oseltamivir for prophylaxis in patients at high risk for complications who were not vaccinated ("high risk patients").

* particularly for pts who are experiencing potentially life threatening influenza illnesses or who are at high risk for serious complications